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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,785	04/20/2001	Ted Lau	51831AUSM1	9790

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Berlex Biosciences
Legal Department
15049 San Pablo Avenue
P.O. Box 4099
Richmond, CA 94804-0099

EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 04/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/838,785	Applicant(s) LAU ET AL	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1-27 and 30-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 28-29 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT, NEW REJECTION

Claims 28-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 28-29 are drawn to a method for selectively destroying a cell expressing SEQ ID NO:2, or a method of treating prostate cancer, comprising administering an immunoconjugate of a monoclonal antibody or fragment thereof, which specifically binds to one or more epitopes of SEQ ID NO2.

The specification discloses a polypeptide sequence of SEQ ID NO:2, which is prostate specific, and expressed in both normal and cancerous prostate tissue, and in metastatic prostate cells (Example 5 on page 43 and figure 6). Further, the specification describes polyclonal and monoclonal antibodies to fragments of SEQ ID NO:2, comprising peptides 4, 5, 7, 8, 10, 11 or peptides of SEQ ID Nos: 19, 20, 21, 23, 24, 26 wherein said antibodies are specific to SEQ ID NO:2 or PROST 03 (Example 4 on

pages 42-43). The specification contemplates immunotherapeutic methods for treating prostate cancer, using an imunoconjugate comprising PROST 03 antibodies and toxic agents (p.31)

There is however no example of *in vivo* killing a cell expressing SEQ ID NO:2 or treating prostate cancer in the specification.

One cannot extrapolate the teaching of the specification to the claims because it was well known in the art at the time the invention was made that although immunotoxins were highly effective as a means of selectively targeting cancer cells, immunotoxins have proved relatively ineffective in the treatment of solid tumors such as carcinomas. WO 93/17715 specifically teaches that (1) solid tumors are generally impermeable to antibody-sized molecules; (2) that antibodies that enter the tumor mass do not distribute evenly because of the dense packing of tumor cells; and (3) antigen-deficient mutants can escape being killed by the immunotoxin and regrow (p. 4, lines 10-37), thus the ability to use the claimed immunoconjugate would be highly unpredictable. Further, as shown in White et al, 2001, Ann Rev Med, 52: 125-145, for a successful immunotherapy, besides the specificity of the antigen, other following properties of the antigen should also be considered: The antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating. Further, antibodies have been developed against a broad spectrum of antigens, and whether the antigens shed, modulate or internalize influence the effectiveness of the administered antibody (p.126, second paragraph). Moreover, antigen internalization or downregulation can cause

repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last).

Further, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method comprising the administration of antibodies specific to SEQ ID NO:2 conjugated to a therapeutic agent would function as claimed. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess

many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method comprising the administration of antibodies specific to SEQ ID NO:2 conjugated to a therapeutic agent would function as claimed. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In addition, it is well known in the art that active immunotherapy in humans is unpredictable. The goal of tumor vaccination is to provide tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability

of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1). Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para2). In addition, Boon teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 112, first paragraph rejection, claim 28 is still rejected under 35 USC 112, first paragraph,because the specification, while being enabling for a method for selectively killing a prostate cancer cell expressing SEQ ID NO:2, does not reasonably provide enablement for a method for selectively killing of a cell expressing SEQ ID NO:2. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 28 is drawn to a method for selectively destroying a cell expressing SEQ ID NO:2, comprising reacting an immunoconjugate of an antibody or fragment thereof, which specifically binds to one or more epitopes of SEQ ID NO2.

Claim 28 encompasses a method for selectively destroying any cancer cell other than prostate cells, and any normal cell expressing SEQ ID NO:2, comprising reacting an immunoconjugate of an antibody or fragment thereof, which specifically binds to one or more epitopes of SEQ ID NO2.

The specification discloses a polypeptide sequence of SEQ ID NO:2, which is prostate specific, and expressed in both normal and cancerous prostate tissue, and in metastatic prostate cells (Example 5 on page 43 and figure 6).

One cannot extrapolate the teaching of the specification to the claims because expression of a sequence in a cancer cell is an unpredictable event, and thus it is unpredictable that any cell other than prostate normal and cancer cells would express SEQ ID NO:2.

Further, MPEP 2164.08(a) teaches that a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claims because the specification disclosed at most only those means known to the inventor. *In re Hyatt*, 708 F.2d 712, 714-715, 218 USPQ 195, 197 (Fed. Cir. 1983). In the instant application, the specification discloses that SEQ ID NO:2 is prostate specific and only expressed in normal and cancer prostate cells, however, the

scope of the claim encompasses a method for selectively destroying any cancer cell other than prostate cells expressing SEQ ID NO:2. Thus the claims would be non-enabled according to MPEP 2164.08(a).

Further, it is not clear what the practical use for selectively killing normal prostate cells.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph rejection, claims 28-29 are still rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method for selectively destroying a cell expressing SEQ ID NO:2, or a method of treating prostate cancer, comprising administering an immunoconjugate of a monoclonal antibody or fragment thereof, which specifically binds to an epitope of SEQ ID NO2, does not reasonably provide enablement for a method for selectively destroying a cell expressing SEQ ID NO:2, or a method of treating prostate cancer, comprising administering an immunoconjugate of "a monoclonal antibody" or fragment thereof, which specifically binds to "one or more epitopes" of SEQ ID NO2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 28-29 are drawn to a method for selectively destroying a cell expressing SEQ ID NO:2, or a method of treating prostate cancer, comprising administering an

immunoconjugate of a monoclonal antibody or fragment thereof, which specifically binds to one or more epitopes of SEQ ID NO2.

Claims 28-29 encompass a method for selectively destroying a cell expressing SEQ ID NO:2, or a method of treating prostate cancer, comprising administering an immunoconjugate of "a monoclonal antibody" or fragment thereof, which specifically binds to more than one epitope of SEQ ID NO2.

The specification describes polyclonal and monoclonal antibodies to fragments of SEQ ID NO:2, comprising peptides 4, 5, 7, 8, 10, 11 or peptides of SEQ ID Nos: 19, 20, 21, 23, 24, 26 wherein said antibodies are specific to SEQ ID NO:2 or PROST 03 (Example 4 on pages 42-43.

There is no example of isolation of a monoclonal antibody that binds to several epitopes on SEQ ID NO:2.

It is well known in the art that although polyclonal antibodies, which comprise a mixture of different antibodies, could bind to more than one epitope on the antigen, a monoclonal antibody is expected to bind only to a single epitope (Ausubel, FM et al, eds, 1987, In: Current protocols in molecular biology, John Wiley & Sons, p.11.0.3).

Thus one of skill in the art would not expect that the claimed monoclonal antibody would bind to more than one epitope of SEQ ID NO2.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

March 27, 2003